

**Comments on**  
**The RoC Background Document for Styrene and Related Documents**

Submitted to  
The Styrene Information and Research Center

By  
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At the request of the Styrene Information and Research Center (SIRC), I reviewed the following documents pertaining to the assessment of the potential carcinogenicity of styrene conducted by National Toxicology Program (NTP) and its peer review group:

1. The RoC Background Document for Styrene (revision dated 9/29/08) (“the revised Background document”)
2. The Styrene Expert Panel Report, Part B – Recommendation for listing status for “Styrene” in the Report on carcinogens and scientific justification for the recommendation (undated) (“the Recommendation for listing status”)
3. The Styrene Subgroup Report for Section 3: Human cancer studies (dated 07/20/2008).

The SIRC asked specifically for comments on the NTP’s interpretation of results pertaining to styrene from the study of synthetic rubber industry workers, conducted by the University of Alabama at Birmingham (UAB). My comments are, for the most part, confined to those sections that refer to the UAB study in the revised Background document and the Recommendation for listing status. Much of the material on the UAB study mentioned in the third document was incorporated into the revised Background document.

## **Comments**

One important conclusion of the Styrene Expert Panel was, “there was limited evidence for the carcinogenicity of styrene in humans...” (Recommendation for listing status, page 2). I agree that the epidemiologic data and other biologic data on styrene are not sufficient for concluding that exposure to this chemical causes cancer in humans.

Another central conclusion of the Styrene Expert Panel was:

“The strongest evidence for cancer in humans is the association between styrene exposure and non-Hodgkin lymphoma (NHL). This evidence comes from the Delzell et al. (2006) analysis in the styrene-butadiene industry and the Kogevinas (1994a) study in the reinforced plastics industry.” (Recommendation for listing status, page 2)

To the extent that the above statement implies that the epidemiologic results for NHL from the two studies constitute strong evidence of a causal relation with styrene, I do not agree. Results for styrene and NHL from both studies are unconvincing.

With regard to the UAB study, the Styrene Expert Panel noted:

“In the Delzell study there was an exposure-response relationship for NHL and NHL plus chronic lymphocytic leukemia (CLL) that was not attenuated by control for butadiene and only mildly attenuated by control for dimethyldithiocarbamate (DMDTC) (which may not have been appropriate to control for). It is very unlikely that such a strong exposure-response trend could be due to chance, bias, or confounding.” (Recommendation for listing status, page 2).

The assertion in the second sentence of the above statement is controversial. As the Background document points out frequently, the papers and report on the UAB study did not include any statistical tests of exposure-response trends for styrene and NHL or NHL/CLL. Such tests have been performed and reported for exposure-response data on butadiene and styrene and leukemia (Delzell et al., 2006, Table 16, page 34), but not for styrene and NHL or CLL-NHL. Among workers with nonzero exposure to styrene, the rate ratio (RR) for NHL rose with increasing levels of cumulative styrene exposure, with butadiene-adjusted RRs of 1.7, 1.8, 2.3 and 3.2 for styrene ppm-years categories of >0-<8.3, 8.3-<31.8, 31.8-<61.1 and 61.1+, respectively (Delzell et al., 2006, Table 18, page 37). However, these data were imprecise, and none of the butadiene-adjusted RRs was statistically significant. The corresponding butadiene-adjusted RRs for CLL-NHL were 2.2, 2.2, 2.7 and 3.1 (none was statistically significant) (Delzell et al., 2006, Table 19, page 37). [The Background document correctly cites these results on pages 125 and 126 (Table 3-3), page 125 *incorrectly* cites the relevant table for NHL and CLL-NHL as 3-2, a table that presents results for leukemia, not NHL or CLL-NHL.]

The latter results for CLL-NHL were driven by the data for NHL. After adjustment for butadiene, there was no evidence of exposure-response for styrene and CLL among those with higher exposure to styrene: in an unpublished “two-agent model” containing terms for age, years since hire, ppm-years of exposure to butadiene (<33.7, 33.7-<425.0, 425.0+) and ppm-years of exposure to styrene (<8.3, 8.3-<61.1, 61.1+), RRs for styrene and CLL were 1.4 (95% CI, 0.4-4.4) for 8.3-<61.1 ppm-years and 1.3 (95% CI, 0.3-5.4) for 61.1+ ppm-years. In this analysis, RRs for butadiene and CLL were 1.3 (95% CI, 0.4-4.1) for 33.7-<425.0 ppm-years and 3.2 (95% CI, 0.8-13.0) for 425.0+ ppm-years. [Pages 124 and 180 *incorrectly* refers to styrene exposure categories as “terciles”; rather, the three categories were (unexposed plus quartile 1), (quartiles 2 and 3 combined) and quartile 4.]

In addition, the elevated RRs for NHL and CLL-NHL among workers with nonzero exposure to styrene reflect, to some extent, unexplained and substantial deficits of deaths from NHL and CLL-NHL in the styrene-unexposed group. These deficits were seen when the workers unexposed to styrene were compared to the general population at large (Delzell et al., 2006, tables 21 and 22). The deficit observed in this “external” comparison was statistically significant for CLL-NHL, based on 2 observed compared to 8.1 expected deaths during the time period 1968-1998 (standardized mortality ratio=0.25, 95% confidence interval, 0.03-0.89). This deficit may have been due to chance, but another possible explanation is the presence of an unidentified confounder. If confounding explains this large deficit of CLL-NHL deaths among workers unexposed to styrene, it is not known if use internal comparison procedures (as done for analyses reported in table 3-3 of the Background document) removed such confounding. The Styrene Subgroup Report for Section 3 (page 3, second paragraph) suggests that the fact that “...workers who survive to go from low to high categories will contribute many person-years to low dose groups as they accumulate dose...could account for the very low SMRs seen in the “0” and lowest dose categories.” The rationale for this explanation is not clear, and the suggested explanation is implausible.

Coexposure to butadiene among synthetic rubber industry workers is another issue that complicates the interpretation of results pertaining to styrene in the UAB study. We found little evidence of an association between butadiene and NHL in the UAB study, but butadiene was associated positively with CLL. Thus, butadiene must be considered as a potential confounder (or, possibly, as an effect modifier) of any association between styrene and CLL or CLL-NHL.

On balance, the UAB study results suggest a positive but statistically imprecise relation between styrene and NHL but no association between styrene and CLL. Thus, if the association with NHL is real, it may be limited to forms of NHL other than small lymphocytic lymphoma. No study has examined this possibility, as it has not been feasible to obtain systematic retrospective data on histopathologic subtypes of NHL in the occupational cohort studies.

The Background document and material from the NTP include fairly extensive comments about the limitations of the epidemiologic information on styrene. These opinions are, for the most part, reasonable. The document notes that data on specific histopathologic subtypes of leukemia and lymphoma, including NHL, are sparse (page 158), that coexposure to butadiene is a potential confounder in the studies of synthetic rubber industry workers and that lack of data on incident cases of lymphoma and leukemia is problematic in most of the available studies of occupational groups. The document's treatment of the issue of DMDTC as a potential confounder also is reasonable.

The document emphasizes the inevitable misclassification of exposure to styrene in the epidemiologic studies, repeatedly stating that such misclassification "...would be expected to be nondifferential and to bias any measures of association towards no effect" (page 161). This statement is not necessarily true in analyses of exposure-response in which RRs are calculated for each exposure category, compared to a nonexposed or lowest exposure referent category. More importantly, a presumably underestimated exposure-response association is not tantamount to evidence supporting a true causal relationship. At most, it may be reasonable to argue that lack of an association in a study with an unusual amount of misclassification does not constitute strong evidence against the existence of a true causal relationship, when there are other studies that support such a relationship.

In the case of styrene and NHL, such supportive epidemiologic evidence is not sufficient for a conclusion of causality. The epidemiologic studies, including the UAB study, are, at best, weakly supportive. The Background document downplays the fact that studies of reinforced plastics industry workers do not provide clear support for a causal relationship between styrene and NHL, citing exposure misclassification, short follow-up, large proportions of short-term employees, etc., as explanations. However, reinforced plastics industry workers on average experienced styrene exposure concentrations much higher than those in the synthetic rubber industry. Even short-term workers in the reinforced plastics industry could have had cumulative styrene exposures similar to, or above, the median cumulative exposure of 17 ppm-years estimated for all styrene-exposed decedents

(or the median of 30 ppm-years among NHL decedents) in the UAB study (Delzell et al., 2006). Thus, the lack of a clear association between styrene and NHL in the studies of reinforced plastics industry workers is an important shortfall of the evidence for the hypothesis that styrene causes NHL. The Background document's argument that the study of Kogevinas et al. (1994a) is supportive of this hypothesis is unconvincing because the Kogevinas et al. study reported that cumulative exposure to styrene was not associated with NHL (only average intensity of exposure displayed a positive association).